This Month in *The Journal*

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Mutant *ICK* in a Multisystem Syndrome

Lahiry et al., pp. 134–147
Intestinal cell kinase (ICK) is a member of the cyclin-dependent kinase family of proteins. Kinases are responsible for phosphorylating other proteins within the body and thereby modifying their activity. Kinases play an important role in numerous cell processes, including proliferation, apoptosis, and cell cycling. Despite its name, *ICK* is expressed in all adult human tissues and is evolutionarily conserved. Using homozygosity mapping and sequencing, Lahiry et al. identify *ICK* mutations in six members of a large Old Order Amish family affected by a multisystem neonatal lethal disorder. Lahiry and colleagues define this recessive disorder as endocrine-cerebro-osteodysplasia (ECO). As the name implies, ECO manifests within the endocrine system, the brain, and the skeletal system. Although ECO does share similarities with syndromes such as Majewski and hydroethalus, it appears to be a distinct entity caused by *ICK* mutations.

Crohn Disease Structure

Chapman et al., pp. 178–187
Many complex traits and diseases are made up of a combination of simpler phenotypes, or subphenotypes. In an effort to simplify complex phenotypes for genetic-association analyses and create more homogeneous case datasets, researchers often look at subphenotypes when studying a disease. Although this allows for easier classification, results can be complicated by the fact that many subphenotypes are correlated with one another. An association between a genetic variant and a subphenotype may indicate that the variant has a direct effect on that subphenotype, or perhaps the variant affects a second subphenotype that, in turn, modifies the first. Chapman et al. report the methods they develop to distinguish direct effects from indirect effects. The authors use simulations to demonstrate the advantages of their methods over using univariate analysis and then look for associations between Crohn disease subphenotypes and gene variants. By evaluating the location of disease and behavior of disease along with the genotype of five variants that have previously been found to be associated with Crohn disease, Chapman et al. report which variants have direct effects on certain Crohn subphenotypes. Similarly, the authors identify which aspects of the disease are highly correlated with one another.

Survey of Nonsense-SNP Variation

Yngvadottir et al., pp. 224–234
Nonsense mutations are alterations that introduce a stop codon into a genetic transcript. This type of mutation often leads to a truncated and usually nonfunctional protein product. Thus, nonsense mutations are widely viewed as disruptive, and many human diseases are the result of such alterations. However, the persistence of such mutations within the genome implicates certain nonsense mutations in improved fitness. Yngvadottir et al. investigate the prevalence of nonsense mutations and thereby shed light on recent human evolution. Their findings indicate that the average person differs from other individuals by about 24 genes as a result of the nonsense SNPs analyzed. Very few of these nonsense SNPs were shown to represent disease-causing alleles. Resequencing of one nonsense-SNP-containing gene, *MAGEE2*, revealed a slight favor for the truncated version of the corresponding CHB protein, implying positive selection of the nonsense SNP. Taken together, these findings encourage an alternate view on the effects of nonsense mutations.

Genetic Genealogy and the Utah Pedigrees

Gitschier, pp. 251–258
As an increasing amount of genetic data is deposited into repositories, there is a concern about how best to protect the identities of those participating in genetic studies. Here, Gitschier reports her efforts to determine how much work is involved in gaining family information about individuals who contributed material for the CEU HapMap samples. Because the Y chromosome is inherited relatively intact through the male lineage, shared Y-chromosome haplotypes can infer direct relationships. Because the CEU samples were collected from Utah and many of the participants were part of the population of the Latter-Day Saints (LDS), the author starts by determining the Y haplotoypes and assembling pedigrees for two leaders of the Latter-Day Saints (LDS) from publicly available genealogy information. She then compares these Y haplotypes to the CEU HapMap samples. None of the samples is a descendent of either of the LDS leaders, but when the CEU haplotypes

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are then compared to the haplotypes in the genealogy information, 20 of the 30 samples hit on perfect matches. From these matches, it is possible for Gitschier to make predictions as to the surnames of those 20 CEU HapMap samples. Although the author does not pursue verifying the accuracy of these predictions, the findings support the need to develop careful ways to maintain anonymity of individuals contributing genetic samples.

Synaesthesia Whole-Genome Scan

Asher et al., pp. 279–285

People who are affected with synaesthesia react in unexpected ways to certain stimuli. For example, some patients perceive colors when they hear sound. The cognitive effects of synaesthesia can vary, and the disorder can lead to dysfunction in language and numerical processing, but also to an improvement in memory and perception. Brain imaging has revealed that unusual regions of the brain are activated in people with synaesthesia when they are exposed to specific stimuli. Unraveling the mechanisms behind synaesthesia will not only contribute to our understanding of the disorder but also add to our knowledge of normal brain function and perception. Although the disorder has been recognized to have heritable qualities, precise knowledge of the pathways that are disrupted has been lacking. Asher et al. report the results of their genome-wide linkage scan in families with auditory-visual synaesthesia. The loci identified might help to pinpoint genes involved in perception.